



4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 73

[Docket No. FDA-2011-C-0878]

Listing of Color Additives Exempt From Certification; Spirulina Extract

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA or we) is amending the color additive regulations to provide for the safe use of spirulina extract made from the dried biomass of the cyanobacteria Arthrospira platensis (A. platensis), as a color additive in candy and chewing gum.

This action is in response to a petition filed by Mars, Inc.

DATES: This rule is effective September 13, 2013. See section X for related information on the filing of objections. Submit either electronic or written objections and requests for a hearing by September 12, 2013.

ADDRESSES: You may submit written or electronic objections and requests for a hearing, identified by Docket No. FDA-2011-C-0878, by any of the following methods:

Electronic Submissions

Submit electronic objections in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.

Written Submissions

Submit written objections in the following ways:

- Mail/Hand delivery/Courier (for paper or CD-ROM submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name and Docket No. FDA-2011-C-0878 for this rulemaking. All objections received will be posted without change to <http://www.regulations.gov>, including any personal information provided. For detailed instructions on submitting objections, see the "Objections" heading of the SUPPLEMENTARY INFORMATION section of this document.

Docket: For access to the docket to read background documents or objections received, go to <http://www.regulations.gov> and insert the docket number(s), found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Felicia M. Ellison, Center for Food Safety and Applied Nutrition (HFS-265), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740-3835, 240-402-1264.

SUPPLEMENTARY INFORMATION:

I. Introduction

In a document published in the Federal Register of January 20, 2012 (77 FR 2935), we announced that Mars, Inc., c/o Keller and Heckman LLP, 1001 G Street, NW., suite 500 West, Washington, DC 20001, had filed a color additive petition (CAP 2C0293). The petition proposed to amend the color additive regulations in part 73 Listing of Color Additives Exempt From Certification (21 CFR part 73) to provide for the safe use of spirulina blue, an extract made from the biomass of A. platensis, as a color additive in candy and chewing gum. We are

establishing spirulina extract as the common or usual name for this color additive instead of the proposed name spirulina blue because it more appropriately describes the additive.

II. Identity, Manufacturing, and Specifications

The color additive that is the subject of this petition is a concentrated aqueous extract from the dried biomass of the cyanobacteria A. platensis, also called spirulina. Spirulina is a blue-green filamentous cyanobacteria that occurs naturally in freshwater and marine habitats. It has a long history as a food in many countries (Ref. 1). Spirulina contains chlorophyll and phycobilins, which absorb sunlight and have a role in photosynthesis. The phycobilins found in spirulina are phycocyanins, which are blue and, together with chlorophyll, give spirulina its characteristic blue-green color.

The petitioner describes the manufacture of spirulina extract using the species A. platensis. Spirulina extract consists primarily of the water soluble components of spirulina, namely phycocyanins and other proteins, polysaccharides, lipids, and minor amounts of components such as vitamins, minerals, and moisture. In general, spirulina extract is manufactured as follows: (1) The spirulina biomass is obtained from grown, harvested, rinsed, washed, and spray dried spirulina; (2) the spirulina biomass is soaked in water to extract the water-soluble proteins; (3) the aqueous extract is filtered and stabilized; and (4) the stabilized filtrate is the color additive spirulina extract. The spirulina extract manufactured by the petitioner contains not less than 10 percent phycocyanins. We have determined that because the amount of the color additive used in food is self-limiting, there is no need for a specific upper limit for the color additive or phycocyanin content (Ref. 2). Therefore, we are limiting the use of spirulina extract in candy and chewing gum to amounts consistent with good manufacturing practice. In addition to specification limits for lead, arsenic, and mercury, we are requiring that

the color additive be negative for microcystin toxin, which is produced by some species of cyanobacteria that could be potentially present in the water where A. platensis is grown and harvested.

III. Evaluation of Safety

Under section 721(b)(4) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 379e(b)(4)), a color additive may not be listed for a particular use unless the data and information available to FDA establishes that the color additive is safe for that use. Our color additive regulations at 21 CFR 70.3(i) define safe to mean that there is "convincing evidence that establishes with reasonable certainty that no harm will result from the intended use of the color additive." To establish with reasonable certainty that a color additive intended for use in food is not harmful under its intended conditions of use, we consider the projected human dietary exposure to the additive, the additive's toxicological data, and other relevant information (such as published literature) available to us. We compare an individual's estimated daily intake (EDI) of the additive from all food sources to an acceptable intake level established by toxicological data. The EDI is determined by projections based on the amount of the additive proposed for use in particular foods and on data regarding the amount consumed from all food sources of the additive. We commonly use the EDI for the 90th percentile consumer of a color additive as a measure of high chronic dietary intake.

IV. Safety of Petitioned Use of the Additive

We have previously considered the safety of the dried biomass of spirulina and certain spirulina-derived substances in food as a result of submissions from firms who have made their own determinations that certain uses of spirulina and spirulina-derived substances in food are generally recognized as safe (GRAS). Under section 201(s) of the FD&C Act (21 U.S.C.

321(s)), a substance is GRAS if it is generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food before January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use. Under section 201(s) of the FD&C Act, a substance that is GRAS for a particular use in food is not a food additive, and may lawfully be utilized for that use without our review and approval. There is no GRAS exemption, however, to the definition of color additive in section 201(t) of the FD&C Act (21 U.S.C. 321(t)). Therefore, we must approve the use of a color additive in food before it is marketed; otherwise the food containing the color additive is adulterated under section 402(c) of the FD&C Act (21 U.S.C. 342(c)).

A firm may voluntarily submit information on a GRAS self-determination to us for review through our GRAS notification program (see 62 FR 18938 (April 17, 1997)). Through this program, we have received four GRAS notices (GRNs) for various uses of spirulina and spirulina-derived substances in food (GRNs 127, 394, 417, and 424).¹ We evaluated each of these GRNs and concluded that we had no reason to question the basis of the notifier's (a person who submits a GRAS notice) GRAS determinations (Refs. 3 to 6). In particular, the spirulina substance that was the subject of GRN 424 is similar in chemical composition to the subject color additive, with phycocyanin content ranging from 42 to 47 percent.

¹GRN 127 pertains to the use of the powdered dried biomass of A. platensis as an ingredient in specialty food bars, powdered nutritional drink mixes, popcorn, and as a condiment in salads, at levels ranging from 0.5 to 3.0 grams per serving. GRN 394 pertains to the use of the powdered dried biomass of A. platensis in certain fruit juices, low calorie fruit and vegetable juice drinks at a level up to 0.3 percent of the food, and in medical foods at a level up to 1.25 percent. GRN 417 pertains to the use of powdered dried biomass of A. platensis in nonalcoholic beverages and beverage bases, breakfast cereals, fruit juices, frozen dairy desserts and mixes, grain products and pastas, milk products, plant protein products, processed vegetables and vegetable juices, snack foods, soft candy, and soups and soup mixes, at levels ranging from 0.5 to 3.0 grams per serving. Lastly, GRN 424 pertains to the use of an aqueous extract of powdered A. platensis or A. maxima as an ingredient for use in all foods at levels consistent with good manufacturing practice, except for infant formula and those (e.g., meat, eggs and catfish) requiring additional review by the U.S. Department of Agriculture. FDA also is aware that spirulina-derived substances are used as dietary ingredients in dietary supplements.

Importantly, in our response to these GRAS notifications, we indicated that if the substances that were the subject of these submissions impart color to the food, they may be subject to regulation as a color additive.

For the petitioned use of spirulina extract to color candy and chewing gum, we focused our review primarily on the safety of the phycocyanins because these pigments are the main coloring components of the additive. As part of our safety evaluation, we estimated the exposure to phycocyanins from current and proposed food uses of spirulina-derived ingredients. We estimate that the petitioned use of spirulina extract in candy and chewing gum will result in an exposure to phycocyanins of 171 milligrams/person/day (mg/p/d) for the 90th percentile consumer 2 years of age or older. Because children typically consume more candy and chewing gum than the general population, we estimated the exposure to phycocyanins from the petitioned use of the subject color additive for children 2 to 5 and 6 to 12 years of age. For these population subgroups, we estimate the exposure at the 90th percentile to be 130 mg/p/d and 185 mg/p/d, respectively. For a cumulative exposure estimate, we used exposure information from GRN 424. The notifier for GRN 424 estimated a conservative exposure to phycocyanins from the notified uses of a spirulina extract to be 1140 mg/p/d. This exposure estimate does not include exposure to spirulina and phycocyanins from dietary supplement use due to the belief that their use is not widespread, and, therefore, would not significantly contribute to the dietary exposure of the wider population. (Ref. 7)

We have concluded that the exposure that was estimated for GRN 424 represents the upper bound cumulative exposure to phycocyanins from spirulina-based ingredients in food because of the high phycocyanin content of the substance that is the subject of GRN 424 (i.e., 42 to 47 percent) and its intended use in most foods (including candy and chewing gum). We

conclude that this cumulative exposure estimate of 1140 mg/p/d for phycocyanins from current and proposed uses of spirulina-derived ingredients is sufficiently conservative (Ref. 7).

To support the safety of the petitioned use of the subject color additive in candy and chewing gum, the petitioner provided a number of published studies that investigated the toxicity of various spirulina powder extracts. The results of these studies showed no toxic effects at the doses that were tested. From these studies, we selected, as the pivotal safety study for this color additive, a chronic feeding study that tested spirulina powder in rats for 21 months at concentrations of 10, 20, or 30 percent of the diet (equal to 5,000, 10,000 or 15,000 milligrams per kilogram bodyweight per day (mg/kg bw/day). We determined that the results of this study showed no indications of adverse effects in rats with prolonged consumption of the spirulina powder at any of the doses tested. Therefore, we concluded that the no-observed-effect-level (NOEL) for spirulina based on the highest dose tested in this study is 15,000 mg/kg bw/d (900,000 mg/p/d for a 60 kilogram person). The phycocyanin content in the spirulina powders that were tested in this study were reported to be in the range of 12 to 20.5 percent and, based on this range, we have determined the NOEL for phycocyanins for humans to be between 108,000 to 184,500 mg/p/d. Taking into account the available safety information, the estimated intake of phycocyanins from the petitioned use of the spirulina extract, and the large margin of safety between the cumulative EDI and the NOEL, we conclude that the proposed use of spirulina extract to color candy and chewing gum is safe (Ref. 8).

We also evaluated the potential allergenicity of spirulina extract. We reviewed a comparison of the known amino acid sequences of phycocyanins with the sequences of known protein allergens and determined that there is a low probability that the phycocyanins are protein

allergens. We conclude that spirulina phycocyanins present an insignificant allergy risk to consumers of the color additive.

Our conclusion regarding the safety of the petitioned use of the color additive is strengthened by the fact that the phycocyanobilin chromophore (the part of the molecule responsible for the coloring effect of the additive) is similar to certain bile pigments that are excreted from the liver via the gall bladder into the intestines. Based on a literature search and review, none of the bile pigments has been reported to produce any toxic effect, except in diseases caused by their presence in the blood due to inborn error of metabolism or other cause.

V. Conclusion

Based on the data and information in the petition and other relevant material, we conclude that the petitioned use of spirulina extract, a color additive made from the biomass of A. platensis, in candy and chewing gum is safe. We further conclude that the additive will achieve its intended technical effect and is suitable for the petitioned use. Consequently, we are amending the color additive regulations in part 73. In addition, based upon the factors listed in 21 CFR 71.20(b), we conclude that certification of spirulina extract is not necessary for the protection of the public health.

VI. Public Disclosure

In accordance with § 71.15 (21 CFR 71.15), the petition and the documents that we considered and relied upon in reaching our decision to approve the petition will be made available for public disclosure (see FOR FURTHER INFORMATION CONTACT). As provided in § 71.15, we will delete from the documents any materials that are not available for public disclosure.

VII. Environmental Impact

We have previously considered the environmental effects of this rule as announced in the notice of filing for CAP 2C0293 (77 FR 2935). No new information or comments have been received that would affect our previous determination that there is no significant impact on the human environment and that an environmental impact statement is not required.

VIII. Paperwork Reduction Act of 1995

This final rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

IX. Section 301(l) of the FD&C Act

Our review of this petition was limited to section 721 of the FD&C Act. This final rule is not a statement regarding compliance with other sections of the FD&C Act. For example, the Food and Drug Administration Amendments Act of 2007, which was signed into law on September 27, 2007, amended the FD&C Act to, among other things, add section 301(l) of the FD&C Act (21 U.S.C. 331(l)). Section 301(l) of the FD&C Act prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FD&C Act (21 U.S.C. 355), a biological product licensed under section 351 of the Public Health Service Act (42 U.S.C. 262), or a drug or biological product for which substantial clinical investigations have been instituted and their existence has been made public, unless one of the exemptions in section 301(l)(1) to (l)(4) of the FD&C Act applies. In our review of this petition, we did not consider whether section 301(l) of the FD&C Act or any of its exemptions apply to food products containing this color additive. Accordingly, this final rule should not be construed to be a statement that a product containing this color additive, if introduced or delivered for introduction into interstate commerce, would not violate section 301(l) of the FD&C Act. Furthermore, this language is included in all color additive final rules

that pertain to food and therefore should not be construed to be a statement of the likelihood that section 301(ll) of the FD&C Act applies.

X. Objections

This rule is effective as shown in the DATES section of this document; except as to any provisions that may be stayed by the filing of proper objections. Any person who will be adversely affected by this regulation may file with the Division of Dockets Management (see ADDRESSES) either electronic or written objections. Each objection shall be separately numbered, and each numbered objection shall specify with particularity the provisions of the regulation to which objection is made and the grounds for the objection. Each numbered objection on which a hearing is requested shall specifically so state. Failure to request a hearing for any particular objection shall constitute a waiver of the right to a hearing on that objection. Each numbered objection for which a hearing is requested shall include a detailed description and analysis of the specific factual information intended to be presented in support of the objection in the event that a hearing is held. Failure to include such a description and analysis for any particular objection shall constitute a waiver of the right to a hearing on the objection. It is only necessary to send one set of documents. Identify documents with the docket number found in brackets in the heading of this document. Any objections received in response to the regulation may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday. We will publish notice of the objections that we have received or lack thereof in the Federal Register.

XI. References

The following references have been placed on display in the Division of Dockets Management (see ADDRESSES) and may be seen by interested persons between 9 a.m. and 4

p.m., Monday through Friday, and are available electronically at <http://www.regulations.gov>.

(FDA has verified the Web site addresses, but FDA is not responsible for any subsequent changes to Web sites after this document publishes in the Federal Register.)

1. M. A. B. Habib, M. Parvin, T. C. Huntington, and M. R. Hasan. 2008. "A Review on Culture, Production and Use of Spirulina as Food for Humans and Feeds for Domestic Animals and Fish." FAO Fisheries and Aquaculture Circular No. 1034. Rome, FAO (<ftp://ftp.fao.org/docrep/fao/011/i0424e/i0424e00.pdf>).

2. Memorandum from N. Belai, Color Technology Team, OCAC, CFSAN, FDA to F. Ellison, Division of Petition Review, OFAS, CFSAN, FDA, December 12, 2012.

3. Letter from L. Tarantino, Office of Food Additive Safety, CFSAN, FDA to J. Dore, Cyanotech Corporation, Agency Response Letter GRAS Notice No. GRN 000127, October 6, 2003, (<http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm153944.htm>).

4. Letter from D. Keefe, Office of Food Additive Safety, CFSAN, FDA to S. Cho, Nutra Source, Agency Response Letter GRAS Notice No. GRN 000394, June 4, 2012, (<http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm313046.htm>).

5. Letter from D. Keefe, Office of Food Additive Safety, CFSAN, FDA to J. Endres, AIBMR Life Sciences, Inc., Agency Response Letter GRAS Notice No. GRN 000417, August 10, 2012, (<http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm319628.htm>).

6. Letter from D. Keefe, Office of Food Additive Safety, CFSAN, FDA to H. Newman, Desert Lake Technologies, LLC, Agency Response Letter GRAS Notice No. GRN 000424, December 6, 2012, (<http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm335743.htm>).

7. Memorandum from D. Folmer, Division of Petition Review, CFSAN, FDA to F. Ellison, Division of Petition Review, CFSAN, FDA, May 31, 2012.

8. Memorandum from G. Erives, Division of Petition Review, CFSAN, FDA to F. Ellison, Division of Petition Review, CFSAN, FDA, October 2, 2012.

List of Subjects in 21 CFR Part 73

Color additives, Cosmetics, Drugs, Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, and redelegated to the Director, Center for Food Safety and Applied Nutrition, 21 CFR part 73 is amended as follows:

PART 73--LISTING OF COLOR ADDITIVES EXEMPT FROM CERTIFICATION

1. The authority citation for 21 CFR part 73 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 342, 343, 348, 351, 352, 355, 361, 362, 371, 379e.

2. Add § 73.530 to subpart A to read as follows:

§ 73.530 Spirulina extract.

(a) Identity. (1) The color additive spirulina extract is prepared by the filtered aqueous extraction of the dried biomass of Arthrospira platensis. The color additive contains phycocyanins as the principal coloring components.

(2) Color additive mixtures for food use made with spirulina extract may contain only those diluents that are suitable and are listed in this subpart as safe for use in color additive mixtures for coloring foods.

(b) Specifications. Spirulina extract must conform to the following specifications and must be free from impurities, other than those named, to the extent that such other impurities may be avoided by good manufacturing practice:

(1) Lead, not more than 2 milligrams per kilogram (mg/kg) (2 part per million (ppm));

(2) Arsenic, not more than 2 mg/kg (2 ppm);

(3) Mercury, not more than 1 mg/kg (1 ppm); and

(4) Negative for microcystin toxin.

(c) Uses and restrictions. Spirulina extract may be safely used for coloring candy and chewing gum at levels consistent with good manufacturing practice, except that it may not be used to color foods for which standards of identity have been issued under section 401 of the Federal Food, Drug, and Cosmetic Act, unless the use of the added color is authorized by such standards.

(d) Labeling requirements. The label of the color additive and of any mixture prepared therefrom intended solely or in part for coloring purposes must conform to § 70.25 of this chapter.

(e) Exemption from certification. Certification of this color additive is not necessary for the protection of the public health, and therefore batches thereof are exempt from the certification requirements of section 721(c) of the Federal Food, Drug, and Cosmetic Act.

Dated: August 6, 2013.

Susan M. Bernard,

Director, Office of Regulations, Policy and Social Sciences,

Center for Food Safety and Applied Nutrition.

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